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The invention relates to the composition of a redox system to the stabilization of certain retinoids in an emulsion with continuous water phase to the topical application. In particular the invention refers to the stabilization of retinol and Retinaldehyd by a particular redox system from Ascorbat/Phenolat (EN) and a particular buffer.

Topical products with retinol (vitamin A) or Retinaldehyd (retinal one) have large interest skilled in the last years, since these affect the differentiation of epithelial tissues. Due to the conjugated Polyensystems the molecules are however to a considerable degree, in particular in presence of water and oxygen, chemical unstable (Clum, C. E. and Wang, J. C. T., Stabilized retinoid containing skin care composition, WHERE 93/00085, 1993). A possibility to the stabilization exists in the technological formulation of the vehicles as anhydrous preparing (Dulak, M. P., and Zecchino, J. R., Anhydrous cosmetic preparations, US 4888363, 1987), water in oil emulsions (Clum, C. E. and Wang, J. C. T., Stabilized retinoid containing skin care composition, WHERE 93/00085, 1993) or emulsions with high proportion (30% and high) of Glycerol (Afriat, I., Gagnebien, D., Stable composition containing A wade-he-sensitive cosmetic and/or dermatological active agent, US 5703041, 1996). These preparing are frequent however unpleasant in the application, since they are pouring sticky, occlusive and, the skin moisture to extract and a fatty glossiness on the skin left can.

An other possibility exists in the use of particular stabilizer systems (Liu et al., retinoid compositions, WHERE 96/07396, 1996). This particular stabilizer system consists of at least a Metallchelator and/or a lipophilic Antioxidanz, if necessary also an hydrophilic Antioxidanz. Those preferred used Metallchelatoren (Natriummethylenediamintetraessigsäure) and lipophilic Antioxidantien (Butylhydroxytoluol) represent synthetic stabilisers, over whose toxicological precariousness lately increased discussed becomes. Instead the use of natural Antioxidantien and synergists offers itself. The anti-oxidative properties of this z. B. Vitamins (tocopherol, ascorbic acid, carotene) are in the best way occupied and them become very wide in the pharmacy, Kosmetik and food industry applied. The anti-oxidative properties of vegetable polyphenols are known. Polyphenols from z. B. the plant Camellia sinensis, show anti-oxidative effect to rapeseed oils (Zandi, P., Gordon, M. H., Antioxidant activity OF extracts from old tea leaves, Food Chemistry 64, 285-288, 1999). Quercetin, a Flavonolaglykon, becomes recommended as Antioxidanz for unsaturated fatty acids in cosmetics (Aebi et al., cosmetics, smelling materials and food additives, George Thieme publishing house Stuttgart, page 14, 1978). Rutin, a Glykosid of the Quercetins, becomes the protection of ascorbic acid derivatives in cosmetic preparing used (Janistyn, H., paperback of the modern Parfümerie and Kosmetik, scientific publishing house company Ltd. Stuttgart, 4. Edition, page 562, 1974). The use of Flavonoiden in cosmetics to the protection of unstable fabrics is subject-matter of a patent application (Iance villages et al., Use OF flavonoids for protecting unstable cosmetic active substances and constituents in cosmetic and dermatological formulations, WHERE 96/18380, 1996). Interactions between the various fabrics, synergistic and inhibitive type, are just as known. In particular the synergism of Rutin and vitamin C is prolonged known with the fight and prevention of scurvy (Rusznayak, S., Szent Györgyi, A., vitamin P: Flavonols as vitamin, Nature 138, 27, 1936). Despite these generally known protective effects of fabrics mentioned no examples are known, became achieved in which by these natural stabilisers a sufficient stability of retinol or Retinaldehyd in topical products. A reason for this lies in the high instability of the natural Antioxidantien. In addition some natural Antioxidantien, z. B. Tocopherol, ascorbic acid, beta - carotene (fox, J., potential and limitations OF the natural antioxidants RRR alpha tocopherol, L-ascorbic acid and beta - carotene in cutaneous photoprotection, Free radical Biology & Medicine 25, 848-873, 1998) or Flavonoide (Ohshima, H. et al., Antioxidant and act ion OF per oxidant flavonoids: effects at DNA damage induced by nitric oxide, peroxyntirite and nitroxyl anion, Free radical Biology and Medicine 25, 1057-1065, 1998) even per-oxidative effects on lipids unfold.

▲ top The preparation of retinoidhaltigen products made usually using inert gas (z. B. Argon) and yellow light. Also for the filling a rinse with inert gas becomes recommended (Clum, C. E. and Wang, J. C. T., Stabilized retinoid containing skin care composition, WHERE 93/00085, 1993). Preparing, those in presence of oxygen, z. B. in packaging means, in particular after its incipient crack, or after the application on the skin stabilize, are the retinoid neither by technological measures, nor by use of stabilizer systems developed became.

The object consisted therefore of it stabilizing bottom renouncement of toxicological disputed stabilisers, retinol and/or Retinaldehyd in a vehicle with continuous water phase, which pleasant is in the application, in particular also in presence of oxygen. The material combinations and vehicles are to be selected with the fact in such a way that per-oxidative effects are prevented.

It was not to be foreseen thus surprising and for the person skilled in the art that a particular combination of at least two pairs of redox, in compound with a particular buffer and particular vehicles would represent according to claim 1 the solution of this object.

Preferred embodiments of this protection system are subject-matter of the Unteransprüche.

Subject-matter of the invention emulsions are contained to the topical application, the particular combination from at least two pairs of redox and a buffer and retinoids chemical stabilize. The term emulsion becomes here used as over term in its broadest sense and describes the distribution of a discontinuous phase in a continuous phase. Both the continuous and the discontinuous phase cannot be present with it liquid, semisolid or solid, but gaseous. Into this sense are also suspensions, creams, ointments, dispersions and solidified emulsions entrapped. The terms of retinoids, retinol, Retinaldehyd and Retinolester will close here in their broadest sense of understood and all trans and isomers (z. B. 13-cis, 9-cis, 9,11-dicis) of molecules. The stability of the retinoids can become by measurement of the initial concentration in the emulsion and the concentration after certain camp intervals certain. The determination of the concentrations can take place after a HPLC method or with UV spectroscopy (German dispensatory 1997, DAB 1997, 12. Output, 1997). As sufficient stable formulations become such understood, which contain than 60% of the initial concentration of the active ingredient after 12 weeks storage with 40 DEG C in sealed glass vessels, which are filled to 1/3 with the preparation and with 2/3 air, still more.

The first ingredient of this redox system is ascorbic acid or a derivative of the ascorbic acid. Derivatives of the ascorbic acid are in particular Dehydroascorbinsäure and esters of the ascorbic acid, z. B. Ascorbylglycoside, Ascorbylpalmitat, Ascorbyldipalmitat, various salts of the Ascorbylphosphate, Dehydroascorbinsäure or other derivatives of the ascorbic acid or mixtures from it. These fabrics become used in a concentration from 0,01 to 15%, in particular in a concentration of 0,1-1,0%, related to the entire emulsion.

A second essential ingredient of this redox system is a polyphenol with a Katecholstruktur, which is conjugated with a Carbonyl carbon atom.

The general structure of these fabrics is in the general formula (I) shown, whereby R stands for n of values between for arbitrary, various or same remainders and can accept 0 and 20.

EMI4.1

Examples of these polyphenols with mentioned structure characteristics are Cynarin, Rosmarinsäure, Ferulasäure, bile acid, Curcumin, Chlorogensäure, Aesculetin, Ellagsäure, Tellimagrandin II, or derivatives of the fabrics. Quercetin, although it corresponds to the general formal one (I), is expressly excluded. US 566367 (citizens et. aluminium, Skin care compositions containing naringinin and/or quercetin and A retinoid, 1997) describes the use of skin care products with a combination from a retinoid and a Naringinin and/or a Quercetin, since these inhibieren synergistically the Keratinozytendifferenzierung. Naringinin does not correspond to the general formula (I). Since Quercetin corresponds to the general formula (I), it becomes excluded for the present invention, although the purpose is the chemical stabilization here. In particular the polyphenol is a Flavonolglycosid with Katecholstruktur. The general structure of these Flavonolglycoside is in the general formula (II) shown, whereby R stands for arbitrary, various or same remainders and a sugar residue represents Gly.

EMI5.1

Examples of suitable fabrics are Troxerutin, Quercitrin, Hyperosid, Diosmin or Rutin. Flavonoide, not by the present invention the detected become are Flavanone and Flavone (the terms defined become in: Boron et al., Interact ion OF flavonoids with ascorbate and determination OF their univalent redox of potential: A pulses radiolysis study, to Free Radicals in Biology and Medicine 19, 45-52, 1995). The concentrations of these polyphenols amount to 0.01 to 15%, in particular 0.1 to 1.0%, related to the entire emulsion. The polyphenols can become also in the form of plant excerpts applied, which contain the specified fabrics. Examples of these plants are Chamomilla types, Calendula types, Camellia types, Arnica types, Fagopyrum types, Saphora types, Citrus types or Gingko biloba. In a preferred embodiment of the present invention two or more of the specified polyphenols become used.

A third essential ingredient of the invention is a buffer to the pH value adjustment. This buffer is the mixture of a weak acid or a weak base with their respective salt. The employment concentration of this buffer is with 0,1 to 30%, in particular with 0,5 to 5.0%. The adjusted pH value is with 7 1.8, in particular with 6,5-7,5. Suitable buffers are tartaric acid/Natriumtartrat, oxalic acid/sodium oxalate, malonic acid/Natriummalonat, citric acid/sodium citrate, polyacrylic acid/sodium polyacrylate or Natriumdihydrogenphosphat/Natriumhydrogenphosphat. Instead of sodium also different salts can become used. Weak basic buffers are in particular organic nitrogen compounds and their salts.

The invention contains particular retinoids. These are polar as Retinolpalmitat and more unstable as Tretinoin. These retinoids are Retinaldehyd, retinol and ester of the retinol with kurzkettigen fatty acids (4 or fewer carbon atoms). Various isomers of these molecules are just as entrapped. The concentration of the retinoids amounts to 0.01-15%. The retinoid is in particular retinol and/or Retinaldehyd.

The redox system, the buffer and the retinoid are in a particular vehicle to the application on the skin. This vehicle is a physical stable emulsion existing from an oil phase, a water phase and fabrics, which increase the physical stability of the emulsion. The water phase of this emulsion is continuous and can z. B. by a rapid solution ability for hydrophilic dyes or by the miscibility with water characterized become. In a preferred embodiment the water phase contains a Gelbildner of the invention and a C5-7-Polyol (z. B. Xylitol, Mannitol or glucose) or an oligosaccharide and a fabric as crystallization eliminators or - timer works. The crystallization eliminator is in particular the not-crystallizing Sorbitollösung 70%. This crystallization eliminator can become by catalytic hydrogenation of starch hydrolysates prepared. Preferred Gelbildner is alginates, cellulose derivatives, xanthan gum, starch, - derivatives, Aerosil< TM > - Types, bentonites, Glycerolmonostearat, poloxamer 127 or polyelektrolytischen polymers, like z. B. Polyacrylic acid, carboxymethyl cellulose or Carrageenan.

This emulsion does not contain preferred Natriumethyldiamintetraessigsäure (NaEDTA) or derivatives of it and no synthetic lipophilic Antioxidantien such as Butylhydroxytoluol (BHT) or Butylhydroxyanisol (BHA). The natural lipophilic Antioxidanz tocopherol interacted disadvantageously with the mentioned redox system and should become therefore in its amount limited. The concentration at tocopherol in the entire emulsion should amount to favourably maximum 5.0%, especially it lies bottom 0.5%. Ester of the tocopherol, like z. B. Tocopherolacetat, can be however in unlimited amount in the emulsion according to invention present.

The emulsion contains favourably 40-95% waters and becomes favourably physical stabilized with emulsifiers. Examples of these emulsifiers are: Myristyl, Cetyl, stearyl alcohol, polysorbates, sorbitan ester, block polymers (z. B. Poloxamers), Glycerolmonofettsäureester (z. B. Glycerolmonostearat), esters of polycarboxylic acids and fatty alcohols, mono and Diglyceride of fatty acids esterified with lactic acid, citric acid or tartaric acid (z. B. Glycerolstearatcitrat), Pemulen< TM > and lecithins and quaternary ammonium compounds (z. B. Cetylpyridiniumchlorid).

The components mentioned can become also as mixtures used. Beside the components mentioned the emulsion can do other cosmetic or dermatological used effect and adjuvants to contain. Examples for this are vitamins, amino acids, vegetable and animal extracts, Antioxidantien, sunscreens, vegetable oils, Antiphlogistika, antimicrobial fabrics, antibiotics, Antipsoriatika, acne means or Corticoide.

The mentioned retinoids are in the mentioned emulsion, even chemical stable in presence of air. In closed glass vessels, which contain 1/3 emulsion and 2/3 air, after 12 weeks storage with 40 DEG C 60% and more of the undecomposed active ingredient are regained.

The subsequent examples are to clarify the present invention, without limiting it. The content regulations became according to the regulation determination of the German dispensatory (German dispensatory 1997, DAB 1997, 12. Output, 1997) made. The content data are always as weight w (earlier: Weight percentage) expressed.

Example 1

In the following the composition of an emulsion according to invention becomes 1 shown, which contains a stabilizer system according to invention. The formulations V1, V2 and V3 are comparison examples and correspond not to the invention.

EMI8.1

The training pairs of redox in emulsion 1 might be Rutin/Rutin radical and ascorbic acid/Dehydrascorbinsäure, eventual mediated over a Monodehydroascorbinsäure radical.

Example 2

The subsequent table 1 compares the stability of the retinol in the formulations not according to invention V1 and V2 (formulations of comparison) of the example 1 with storage as far as possible without air in aluminum tubes (RK) and in closed glass vessels (GG), which contain 1/3 of the emulsion and 2/3 air. The values are in percent of the initial concentration indicated. The storage made with room temperature (blank) and 40 DEG C, the pH value amounts to 6.

Table 1

EMI9.1

The table 1 shows that ascorbic acid can improve alone the Retinolstabilität, in presence of oxygen the stability however unsatisfactory is and the stabiilités significant defined in this invention are missed.

Example 3

The influence of Rutin on the Retinolstabilität can become the table 2 removed. Formulation V3 contains only Rutin and no ascorbic acid and is not thus not according to invention. The formulation 1 contains however ascorbic acid and Rutin and is thus composed according to invention. The storage made in closed glass vessels, the 1/3 of the emulsion and 2/3 air contain and values of the pH amount to 6. The values are in percent of the initial concentration expressed.

Table 2
EMI10.1

The table 2 shows that Rutin, contrary to which claims from WHERE 96/18380 (Iance villages et al., Use OF flavonoids for protecting unstable cosmetic active substances and constituents in cosmetic and dermatological formulations, 1996) in the formulation V3 retinol works not stabilized, rather even per-oxidative. Only as ingredient of the redox system according to invention, in compound with the particular buffer and vehicle, Rutin improves the stability of the retinol (1).

Example 4

This example shows the influence of the pH value of the buffer to the Retinolstabilität. For this the buffer on pH became 4.5, 6.0 and 7.5 adjusted. The results of the formulation according to invention 1 are in table 3. The storage made in closed glass vessels, which contain 1/3 of the emulsion and 2/3 air. The values are in percent of the initial concentration expressed.

Table 3
EMI10.2

The table 3 shows that the redox system is not effective with use of an acidic buffer (pH 4.5). Only buffering in the neutral pH range (6.0 and 7.5) leads too much good stabilities.

Example 5

The invention refers to emulsions with continuous water phase. As comparison example became water in oil an emulsion V4 prepared. This vehicle does not become detected of the invention.

EMI11.1

In the table 4 the stability of retinol in the water in oil emulsion V4 with the stability of the oil in water emulsion is 1 compared. The storage made in closed glass vessels, the 1/3 of the emulsion and 2/3 air contain and the pH value amount to 6. The values are in percent of the initial concentration expressed.

Table 4
EMI12.1

The table 4 shows that only the vehicle according to invention 1 with continuous water phase the object of the stabilization of the retinol met.

Example 6

This example shows the influence of Metallchelatoren and synthetic lipophilic Antioxidantien. For this the preparation according to invention 1 either 0.1% Natriumethylenediamintetraessigsäure (2) became, or 0.1% Butylhydroxytoluol (3) or 0.1% Natriumethylenediamintetraessigsäure and 0.1% Butylhydroxytoluol (4) added. After the claims from WHERE 96/07396 are these necessary essential to the stabilization. With use of the present inventions, becomes achieved contrary to the claims mentioned, no other stabilization. Table 5 shows that without the toxicological precarious stabilisers can be done. The storage made in closed glass vessels, the 1/3 of the emulsion and 2/3 air contain and the pH value amount to 6. The values are in percent of the initial concentration expressed.

Table 5
EMI12.2

The examples have shown that only a particular redox system, and this are able to stabilize only in combination with a particular buffer in a particular vehicle, the active ingredient retinol in presence of oxygen.

Altogether seen unite the emulsions according to invention with redox system the subsequent advantages. It concerns an emulsion with continuous water phase, which opposite water in oil emulsions or anhydrous preparing in the application are more pleasant. The use of the emulsions with redox system the allowed renouncement of synthetic Antioxidantien, in particular on the toxicological precarious Butylhydroxytoluol (BHT) and Natriumethylenediamintetraessigsäure (NaEDTA). The specified retinoids are in the present invention in presence of oxygen stable. Therefore can on the increased technical effort of a preparation and filling of the products bottom inert gases (z. B. Argon) to be done without.